Controlled Release of Antimicrobial Surrogate Can Be Imaged Over 7 Days In Vivo.

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Statement of Purpose: Controlling biofilm-based, periprosthetic joint infection and surgical site infections relies on the use of local antimicrobial delivery combined with surgical debridement. Clinically, ALBC (antimicrobial loaded PMMA bone cement) are used to control release of high local doses of antimicrobial and control active infection. Clinical formulations of ALBC range from 1.6wt% antimicrobial (commercially available) to 21wt% antimicrobial (physician directed use). Existing methods for determination of delivery efficacy rely on measurement of blood concentrations, tissue biopsies, and other laboratory based techniques that are time consuming and not comprehensive. We have previously reported on the use of MRI to visualize surrogate delivery in a non-surgical model(1). The goal of this study is to trace an antimicrobial surrogate, gadolinium 3^+ diethylenetriaminepentaacetic acid (Gd-DTPA), to determine the distribution of locally delivered agent over a period of 7 days.

Methods: This study employs 2.9wt% Gd-DTPA as the payload, with 11wt% of Xylitol as a particulate poragen, to improve efficiency of Gd-DTPA release. A PTFE mold is used to form the ALBC into 1cm cubes or 4mm diameter by 1cm length cylinders.

Two different types of wounds are created. In both, an incision is made over the anterolateral thigh of a New Zealand White Rabbit. For the first type of wound, 1g of muscle is removed from the thigh using a ronjeur. A 15mm long by 3mm wide cortical bone window is made in the femur using a 5mm acorn burr. Pre-formed rods are then inserted proximally and distally into the femoral canal through the bone window. A 1 cm cube is then inserted, and only the skin is closed with suture. For the second type of wound, there is no bone defect or rods, and the muscle, fascia, and skin are all closed with suture. Post-surgically, the animal is scanned once per day on a Bruker Biospin 7T MRI, using a series of RARE scans (TE=9.0ms, TR=1000,1500,3000,5000ms). Image series are converted to T1 maps using the Bloch Equation, and cleaned with a median filter. Subsequently, images are thresholded, and 3D volume maps and 2D concentration maps are constructed with the use of Mimics and MATLAB, respectively. Volume maps are constructed to a threshold of approximately 14µg/mL. The animal is euthanized at the end of 7 days.

Results:

Figure 1 shows reconstructions from Mimics for one animal. A left femur fracture developed between 1 hour and 1 day post-surgical scanning. The fracture was managed with observation and buprenorphine, and the experiment continued despite the fracture.

Both wound model types show maximal soft tissue delivery at 1 hour, with the volume of delivery decreasing asymptotically over the first 5 days. There is little difference in the overall volume of distribution of contrast agent. By the 5th day, the volume of distribution in the image has contracted to nearly the volume of the depot. Upon post-mortem examination, all rods and cubes were found as they were placed in surgery.

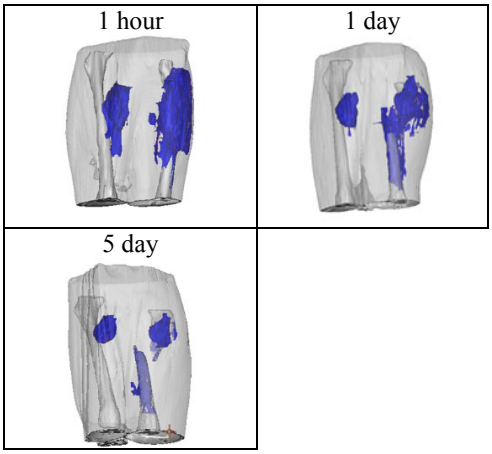

Figure 1: Local Distribution of Contrast Agent around Local Delivery Vehicle. The blue area represents the volume of tissue with concentration >14 µg/mL. The animal's left leg is the full model, and the right leg is the partial model.

Conclusions: Our results disagree with the results of Adams et al., who showed local antimicrobial delivery in dog tibia with a window defect persisted 28 days. (2) The results above are consistent with bench-top elution data for ALBC, which shows the period of greatest release to occur between 1 and 3 days. The large volumes containing contrast at 1 hour and anisotropy of distribution suggests convection plays a larger role in antimicrobial distribution post-surgically than previously appreciated. Comparing this study, done primary in muscle, to Adams et al., primarily in bone, local drug delivery may rely heavily on the delivery environment. We hope to replicate these findings with tagged antimicrobials in the near future.

References:

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